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Wound healing

Injury triggers an organized and complex cascade of cellular and biochemical events that result in a healed wound. The mechanisms and stages of wound healing are more or less the same in different tissues with minor variations

Components of wound healing

1. Wound contraction. This process of contraction helps to diminish the size of the wound. It starts immediately after wounding and continues for the next 2-3 weeks. It is assumed to be due to special myofibroblasts, which contain the smooth muscle protein actin.
2. Granulation tissue formation, which is later replaced by fibrous tissue.
3. Epithelialization.

All three components share in healing of all wounds, but in a proportion and timing that differ according to the type of wound.

- Clean sutured wounds epithelialize in about 48 hours. Both wound contraction and granulation tissue fibrosis occur to a little extent and at a later date.
- If wound edges are wide apart, wound contraction and granulation tissue fibrosis have larger contributions, while epithelialization covers the surface when the gap is filled to the surface with granulations.

Stages of wound healing

Wound healing response can be divided into three overlapping phases .

[A] Haemostasis and inflammation phase

1. Injury of blood vessels in the wound leads to aggregation of platelets to the sub endothelial collagen and activation of the coagulation cascade.
2. From the platelets certain cytokines and growth factors are released and these stimulate chemotaxis of leucocytes, macrophages and lymphocytes
3. Macrophages play an important role in phagocytosis and wound debridement. They release further growth factors, which lead to recruitment and activation of fibroblasts and endothelial cells.

This phase lasts for about 5 days, but it may be prolonged if there is wound infection.

[B] Proliferation phase

This phase is characterized by the proliferation of

1. Fibroblasts which are derived from the surrounding tissues. They secrete collagen fibers.
2. Endothelial cells which proliferate from the intact venules to form new capillary buds, which together with the fibroblasts form the granulation tissue.

3. Epithelial cells which proliferate from the wound edges and injured epithelial islands within the wound. The basal cells of the epidermis start to undergo hypertrophy and mitosis and start migration to close the epithelial defect. In large open wounds the epidermis grows for few centimeters and then slows down and a raw area will persist.
   In any type of wound the young epithelium is thinner than normal epithelium and it possesses no sebaceous or sweat glands, nor hair follicles.

[C] Maturation and remodeling phase

1. Deposition of collagen in the wound: Collagen III is deposited at first, but over the next weeks collagen III decreases while collagen I increases.
2. Remodeling: With time the collagen fibers become thicker and they get arranged along the lines of stress leading to an increase in the tensile strength of the wound. The process of remodeling continues for about one year. It should be noted that a wound never attains its full original tensile strength.

Types of wound healing

1. Healing by primary intention: This occurs in clean wounds when they are immediately closed by sutures or clips. Healing occur with minimal fibrosis leading to a nice neat scar .
2. Healing by secondary intention: This occurs when the wound edges are not approximated or when gaping occurs as a result of a haematoma or wound infection. Healing occurs by in-filling with granulation tissue and so there is more fibrous tissue. The resulting scar is ugly.
3. Healing by tertiary intention: Wounds which are contaminated are left open for about 5 days. At the end of this period if there are no signs of infection, delayed primary sutures can be performed.

It is to be noted that many cells, growth factors and cystokines participate in the process of wound healing

- **Cells:** Platelets, polymorph nuclear leucocytes, macrophages, lymphocytes, fibroblasts, endothelial cells and epithelial cells.
- **Growth factors and cytokines:** Platelet derived growth factor, tumor necrosis factor-alpha, interleukin-I and fibroblast growth factor.

Fluids, Electrolytes, Acid – Base Balance

Body water

- The total body water varies from 45-75% of the body weight, depending on the body content of fat.
  - An adult male contains 60% water
  - a female having more fat contains 55% water,
  - a newborn infant has 75% water.
- The total body water is divided into
  1. intracellular compartments (2/3)
  2. Extracellular (1/3)
     - interstitial compartment
     - intravascular compartment which is the plasma
- Water freely distributes through all body compartments to bring the osmolarity of all compartments into equilibrium.
- The sources of water in the body are either exogenous or endogenous.
  - Exogenous water intake is provided either by drinking or ingestion of solid food. The input varies widely, but averages 2-3 litres per day, of which slightly less than half is contained in solid food.
  - Endogenous water is released during the oxidation of carbon dioxide, and is known as metabolic water which amounts to 350 ml water per day.
- This total water input is normally balanced with the water output from the body. Water is lost from the body by four routes (lungs, skin, feces and urine).
  1. Lungs: About 400 ml of water is lost in expired air each 24 hours and is greater with increased respiratory rate.
  2. Skin: Water is lost through the skin by two mechanisms
     a) obligatory insensible perspiration containing virtually no sodium
     b) active sweating rich in sodium depending mainly on climatic conditions.

     In a temperate climate, the average insensible obligatory water loss is between 600-1000 ml per day.
  3. Faeces : Between 60-150 ml of water are lost by this route daily and is increased with diarrhea.
  4. Urine. The output of urine is under control of multiple influences, such as blood volume, hormonal and nervous factors, the most important of which is the antidiuretic hormone (ADH). The amount of water excreted in urine varies after the previous three routes have been met. The normal urinary output is approximately 1500 ml/day. A minimum urinary output of about 400 ml/day is required to excrete the end products of protein metabolism.

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Electrolyte metabolism

- Sodium is the main extracellular cation and potassium is the main intracellular cation. The normal serum electrolyte levels are roughly
  - Cations : Na = 142 mmol/L K 4 mmol/L
  - Anions : Cl = 103 mmol/L HCO3 25 mmol/L
- Under normal conditions, the number of anions must equal the number of cations to keep the electrochemical neutrality of the ECF.
  - The main cations are sodium and potassium.
  - The main anions are chloride, bicarbonate, phosphates, sulphates, proteins and organic acids.
- Practically HCO3 and Cl are the anions that are measured in the laboratory. Thus, when we add the normal values for these, they are less than those of the cations. The difference is known as the **Anion Gap**, and represents the other anions that are not usually measured.
- The interstitial fluid content is similar to plasma but with very low protein and a slightly higher chlorides.

Sodium

- Sodium is the main extracellular cation. It plays a central role in maintaining blood volume.
- There is normally a balance between sodium intake in the diet and its output mainly in urine, some in feces and a negligible amount in insensible perspiration. However, in hot climate, profuse sweating results in a considerable loss of sodium.
- The average daily intake of sodium is 1 mmol/kg, which is about 5 gm/day, equivalent to 500 ml of isotonic 0.9% saline solution.
- Sodium balance is largely controlled by regulating its output which is governed by the variation in the avidity with which the renal tubules reabsorb sodium from the glomerular filtrate and the amount of sodium excreted by the sweat glands. This is under the control of the adrenal corticoids; the most powerful conservator of sodium being aldosterone.
- Obligatory reduction in sodium excretion follows surgery or trauma for a period of about 48 hours due to increased adrenocortical activity. It is inadvisable to administer Large quantities of isotonic saline (0.9 %) solution immediately after surgery for about 2 days.

Potassium

- Potassium is the major intracellular cation.
- Abnormalities of potassium concentration are of concern because of the risk of cardiac arrhythmias.
- The normal daily potassium intake is about 1 mmol/kg, mainly in potassium-rich food such as fruit, milk and honey.
- Potassium excretion is mainly in urine and almost equals the intake. A very small quantity is lost in formed feces and still a smaller quantity in sweat.

- Augmented potassium excretion follows surgery and trauma. There is a period of increased excretion of potassium by the kidneys varying directly with the degree of tissue damage. This loss is greater during the first 24 hours and lasts for about 3-4 days. So great are the reserves of potassium that, unless the patient is severely depleted at the time of operation, hypokalaemia may not reveal itself for 48 hours.

Calcium

- The majority of body calcium is found in bones in form of phosphate and carbonate.
- The remainder is present as an extracellular cation which exists in almost equal two forms
    1. Ionized free fraction, which is responsible for the biologic effects of calcium, such as the neuromuscular stability, blood coagulation and cellular enzyme processes.
    2. Non-ionized protein-bound, chiefly albumin.
- Determination of the plasma protein level is essential for proper analysis of the serum calcium level. A low albumin level gives a false low total serum calcium concentration and vice versa.
- The ratio of ionized to non-ionized calcium is related to the PH acidosis causes an increase in the ionized fraction, whereas alkalosis causes its decrease; respiratory alkalosis due to hyperventilation results in tetany with an apparently normal total serum calcium level.
- The normal serum level is between 8.5 and 10.5 mg/dl (4.25-5.25 mEq/L or 2.2-2.5 mmol/L).
- The serum calcium level is likely to be modified by vitamin D, parathormone, calcitonin and the state of renal and small bowel function.

Acid-base regulation

- The normal ECF pH is 7.4 +/- 0.04 , and most enzymatic processes operate only within a narrow pH range (7.3-7.5).
- Normal metabolism produces approximately 15000 mEq H^+/day.
- Mechanisms for the regulation of body pH can be divided into three categories

1. Body buffer systems (pH shock absorbers): The most important of these systems is the bicarbonate -carbonic acid ratio, which is normally 20:1. Alteration in this ratio changes the pH regardless of the absolute values of the bicarbonate and carbonic acid. A decrease in the ratio leads to increased acidity and vice versa.
    - The bicarbonate level can be changed by metabolic factors,
    - Carbonic acid level is subjected to alteration by respiratory factors.
    - Alteration of one is followed automatically by a compensatory change in the other in an attempt to keep this ratio and pH constant.
2. Renal regulation (works in hours and days) These function to maintain body pH by:
    - Reabsorbing filtered bicarbonate.
    - Excreting 50-100 mmol of H^+ /day.
    - Renal failure is associated with a state of chronic acidosis.

3. Respiratory regulation (works within minutes): This occurs by elimination of CO_2, which is the source of carbonic acid. Since CO_2 diffuses approximately 20 times more readily than O_2, severe respiratory impairment must occur before CO_2 retention occurs.

Haemorrhage and Shock

Physiological response to haemorrhage

The physiological response to haemorrhage has two aims:

[A] Stopping the bleeding

1) Vasoconstriction and retraction of the intima of the injured vessel.
2) Platelet plug.
3) Blood clotting.

These mechanisms occur in sequence. They are more effective when the vessel is completely transected than when there is a side tear, and in traumatic than in pathological cases when constriction of the vessel may be hindered by inflammatory or degenerative changes in the vessel wall or in its surroundings, e.g., the fibrous tissue in the base of a bleeding chronic peptic ulcer.

[B] Maintaining effective circulatory volume and perfusion of critical tissues (brain and heart), at the expense of less critical tissues (skin, skeletal muscle and splanchnic area). This is achieved by neural and endocrine factors.

A. Neural factors.
    1. A sympathoadrenal discharge develops due to decrease in stimulation of arterial baroreceptors (aortic arch and carotid sinus) and atrial stretch receptors leading to reduction of the normal inhibitory discharge in the vagus and glossopharyngeal nerves on the vasomotor centre with consequent stimulation of the sympathetic system. The effects include constriction of veins, which normally contain two-thirds of the blood volume displaces blood from the capacitance side of the circulation into the heart.
    2. Constriction of arterioles raises the peripheral resistance but this is not uniform. It involves mainly the arterioles of the skin, skeletal muscle, and splanchnic area. Perfusion of the heart and brain is maintained because their metabolic needs override the alpha adrenergic vasoconstrictor discharge.
    3. Increased rate and strength of cardiac contraction.

B. Endocrine factors
    1. Catecholamine discharge
        a. occurs from the adrenal medulla and from the nerve endings throughout the autonomic nervous system.
        b. They increase the heart rate and myocardial contraction and cause constriction of the arterioles of the skin, kidney and viscera.
    2. The metabolic hormones ACTH, cortisol, growth hormone and glucagon are increased. insulin release is inhibited by adrenaline and noradrenaline.
    3. The renin-angiotensin aldosterone system:

a. The juxtaglomerular cells of the afferent renal arterioles secrete renin in response to renal hypoperfusion. Renin splits angiotensinogen to angiotensin I which is converted to angiotensin ll by a converting enzyme in the lung.
b. Angiotensin ll is a powerful vasoconstrictor and stimulates sodium and water retention by a direct action on the kidney as well as indirectly through release of aldosterone from the zona glomerulosa of the adrenal cortex.
c. Angiotensin mediated vasoconstriction takes some 20 minutes to occur, whereas baroreceptor-vasoconstriction occurs within seconds.

4. ADH (vasopressin):
   a. Blood loss greater than 10% stimulates ADH release.
   b. ADH increases the permeability of the renal collecting tubules allowing water absorption into the hypertonic renal medullary interstitium.
   c. With severe haemorrhage high levels of ADH also cause vasoconstriction.

C. Transcapillary refill
   a. Reduction of blood volume and constriction of arterioles causes a fall in capillary hydrostatic pressure and promotes movement of fluid from the interstitium into the capillaries.
   b. The resulting haemodilution increases the blood volume and lowers its viscosity, thus improving effective circulatory volume.

Natural haemostasis

Primary haemostasis

- Arrest of haemorrhage within the first few minutes is achieved by

1. Vasoconstriction of the disrupted vessels. This is achieved by
   - Contractile proteins in the endothelium (even capillaries constrict).
   - Neurogenic reflexes.
   - Direct smooth muscle stimulation (spasm).
   - Vasoconstrictors , e.g. thromboxane.
   - Vasoconstriction is more efficient in arteries than veins because arteries contain more muscular fibers. Vasoconstriction is less effective in the following conditions
     a) When a vessel is partially injured.
     b) In stiff atherosclerotic vessels.
     c) In large veins (poor muscle coat).
2. Platelet plug. Platelets serve the following haemostatic functions
   - Adhere to exposed subendothelial collagen.
   - Release the contents of their granules, e.g. ADP, and serotonin.
   - Aggregate to form a plug that seals the bleeding vessel. Thromboxane from platelet membrane phospholipids, ADP, serotonin , thrombin etc. are responsible for aggregation.
   - Platelet phospholipids has a vital role in blood coagulation.

3. Tamponade of the bleeding by surrounding tissue tension. Interstitial haemorrhage tends to be less profuse than external or internal haemorrhage.

Secondary haemostasis

- Maintenance of haemostasis after the first few minutes requires that the platelet plug be reinforced by fibrin deposition. i.e. coagulation. Coagulation is activated by two mechanisms :
    1. Extrinsic: initiated by activation of factor VII upon admixture of plasma and tissue factor.
    2. Intrinsic: initiated by activation of factor XII upon contact with a non-endothelial surface, more directly by activation of factor IX through activated factor VII.
- Sequential activation occurs locally; any activated coagulation factor spilling into the general circulation is neutralized by inhibitors such as antithrombin III and proteins C and S. deficiency of these proteins may cause spontaneous thrombosis, e.g. mesenteric vascular occlusion.

Fibrinolysis

- Once haemostasis is achieved. The clot obstructing the vessel is no longer needed. Circulating plasminogen and tissue plasminogen activator bind to the fibrin clot leading to local formation of plasmin which digests the clot and restores vascular patency .
- Circulating inhibitors neutralize plasminogen activators and plasmin which form or overflow into the circulation.
- The products of fibrin digestion by plasmin are called fibrin degradation products (FDP).
- D-dimers result from plasmin cleavage of cross linked fibrin and constitute a marker of fibrinolysis.

Pathophysiology of Haemorrhagic Shock

The classical example of hypovolaemic shock is haemorrhage.

[A] The sympatho-adrenal response

- The body response to haemorrhage aims to stop the bleeding and to divert blood from the relatively less critical tissues (skin, gastrointestinal tract and the kidney) to the critical organs as the brain and the heart. Both neural and endocrinal factors work together in super harmony to fulfill this function.
- The clinical picture of a patient with hypovolaemic shock is a reflection of this intense sympathoadrenal response. If the patient is rapidly treated by adequate volume replacement, vital signs will return to normal and he will be fine. With persistent hypovolaemia or lack of prompt treatment, the intense sympathoadrenal response starts to produce harmful effects as follows

[B] Microcirculatory changes

- Under the effect of catecholamine : The precapillary sphincters constrict→ Less blood enters the capillaries → the capillary circulation becomes sluggish.
- Untreated hypovolaemia → hypoxia.
    - Under normal conditions only one third of the capillary bed is open at a time.
    - Under ischemic conditions, however, the body reacts by opening more capillaries. The results are:

- Further slowing of capillary circulation, the so called sludging of blood.
- Sludging encourages spontaneous coagulation of blood in these capillaries. If extensive, it is called disseminated intravascular coagulation (DIG). This depletes coagulation factors and induces bleeding tendency in the rest of the body (consumption coagulopathy).

- A sluggish circulation and DIC compound tissue hypoxia and affect the function of capillary endothelium→ leakage of large protein molecules from the vessels into the interstitial space→ dragging with them huge amounts of fluid. This third space loss of fluid→reduces the blood volume.

Knowledge of this sequence of events reflects the importance of early restoration of adequate blood volume.

[C] Cellular Derangement

- Lack of oxygen forces the cells to rely on anaerobic glycolysis for the production of energy and ATP.
- Anaerobic metabolism produces lactic acid and a small amount of energy, with persistent hypoxia, cellular demand exceeds production of energy→cellular functions deteriorate.
- Most important is the failure of Na/K pump which results in inability of the cells to get rid of sodium with consequent progressive accumulation of intracellular water.
- The end result is rupture of lysosomal and plasma membranes and cell death.
- Though the vital organs are originally spared as a result of the sympatho-adrenal response, they are eventually exposed to hypoxia. If extensive cell death affects these organs→ irreversible shock.

[D] Acid-base imbalance

Shock is accompanied by metabolic acidosis, which is caused by

1. Accumulation of lactic acid as a result of anaerobic metabolism. Initially the body tries to correct acidosis by the buffering system, by hyperventilation, and by renal conservation of bicarbonate.
2. Renal failure from prolonged ischemia, aggravates acidosis.

[E] Individual organs

1. *Heart:* Myocardial contractility is impaired by:
   a. The reduction in coronary arteries perfusion.
   b. Direct myocardial depressants as :
      i. Cachectin “tumour necrosis factor” (TNF) released from the hypoperfused gut.
      ii. Leukotrienes
      iii. Platelet activating factor that are released in trauma.
2. *Gastrointestinal tract :*
   a. The mucosa is the most sensitive layer to ischemia.
   b. Ischaemia of the gastric and duodenal mucosa may produce superficial ulcers, the so-called “stress ulcers” which may bleed.

c. The normal colon mucosa does not allow invasion of the blood stream by its microorganisms. With persistent hypoperfusion of the bowel, there may be translocation of bacteria and endotoxins from the lumen into the circulation. This phenomenon plays a role in septic death in previously, shocked patients even after resuscitation.

3. *Liver:* Ischemic hepatic dysfunction is a frequent component of multiple organ system failure in patients who survive initial therapy.
4. *Kidneys :*
   a. Total renal blood flow decreases due to the sympathoadrenal response.
   b. Intrarenal distribution of blood flow shifts from the cortex to the medulla.
   c. Renal renin leads to increased levels of angiotensin ll which is a potent vasoconstrictor, releases aldosterone and antidiuretic hormone.
   d. The net effect is to decrease glomerular filtration rate and increase tubular reabsorption of salt and water in an attempt to maintain the circulating intravascular volume deficits.
   e. Prolonged hypotension ends in acute tubular necrosis (ATN) which is a part of the multiple organ system failure.
5. *Lungs:* ARDS .

Pathophysiology of Septic Shock

When bacteraemia produces changes in circulation such that tissue perfusion is critically reduced. septic shock develops. This type of shock is the end result of numerous complex interactions between exogenous and endogenous mediators on one side, and the host response to these mediators on the other side.

[A] Mediators cascade

- The bacterial endotoxin generated by the infecting organisms triggers complex immunological reactions. This endotoxin is the lipopolysaccharide part of the cell wall of Gram-negative bacilli that is liberated from the dead bacteria.
- Endotoxin stimulates macrophages and Kupffe cells of the liver to release cytokines. These are large peptides whose normal function is communication to mediate a useful inflammatory response. In huge amounts, however, they have harmful effect on the microcirculation, particularly on the capillary endothelium. Some of these mediators are
  - Tumour necrosis factor (TNF).
  - Interleukines.
  - Platelet activation factor.
  - Prostaglandins (prostacyclin and thromboxane).
  - Nitric acid which is one of the free oxygen radicals and is also a strong vasodilator.

[B] Microcirculation

- Septic shock is initially caused by maldistribution of cardiac output. Under the effect of cytokines vasodilatation of the arteries occurs and arteriovenous shunts are opened. The results are:
  a. Reduced peripheral resistance. Nitric acid → more reduction in the peripheral resistance.

b. Capillaries are bypassed and blood is shunted in the oxygenated form from the arteriolar to the venular side.
c. Oxygen delivery to the tissues is impaired.

- Disseminated intravascular coagulation (DIC) is the result of
    a. Sluggish capillary circulation.
    b. The action of platelet activation factor.
- Vascular endothelial damage under the effect of cytokines is the dominant harmful feature of septic shock.
- The result is leakage of protein-rich fluid from the circulation into the interstitial space → Edema.

[C] Cellular Derangement

1) Oxygen delivery is reduced because of
    a. Maldistribution of blood (main factor).
    b. Late pump failure.
    c. Hypovolaemia.

   When the delivery is reduced below a certain critical level oxygen uptake by the cell is also impaired.
2) Oxygen uptake and utilization by the cells is also directly suppressed by the toxins. The sequence of events that lead from hypoxia to cell death are the same as described under hypovolaemic shock but they proceed at a faster rate.

[D] Acid-base imbalance

- As in hypovolaemic shock, there is excess production of lactic acid which produces metabolic acidosis. The body tries to compensate by hyperventilation to wash out CO_2 and by renal conservation of bicarbonates to buffer the acid. These measures temporarily restore pH . Ultimately the kidneys are overwhelmed and fail resulting in the production of frank metabolic acidosis.
- The usual changes in arterial blood gases (ABGs) are
    - Low pH (lactic acidosis).
    - Low PO_2 < 70 mm Hg (respiratory distress then failure).
    - Low PCO_2 (hyperventilation).
    - Low HCO_3 (depleted buffers).

[E] Individual systems and organs

The heart, brain and kidneys are normally protected from swings in blood pressure by autoregulation. In late sepsis, however, these mechanisms fail. In septic shock multiple organ failure (MOF) proceeds faster than in hypovolaemic shock.

Heart:

- The heart is privileged by its auto-regulatory mechanisms which maintain coronary blood flow and keeps its ability to extract oxygen in the face of low oxygen delivery level.

- Initially the heart compensates by increasing its rate and force of contraction, in an attempt to increase the cardiac output and consequently the oxygen delivery to the cells.
- If septic shock is inadequately treated heart failure takes place because of
    - Direct effect of some cytokines, e.g. TNF and leukotrienes on the heart.
    - Reduced coronary flow when the blood pressure becomes very low.
    - Increased oxygen demands of the cardiac muscle because of over-work.

Lungs:

- Adult respiratory distress syndrome (ARDS) is a common sequel of septic shock. The generalized capillary endothelial damage leads to alveolar and interstitial edema. The results are:
    - Reduced compliance, and alveoli that are filled with fluid Both affect ventilation
    - Opening of arteriovenular shunts →divert blood away from the capillaries impairs perfusion.
    - Interstitial edema widens the space between blood in the capillaries and air in the alveoli, the so-called thickened alveolo-capillary membrane .This in addition impairs gas diffusion.
- The three components of respiration (ventilation, perfusion and diffusion) are thus impaired and ultimately lead to respiratory failure

Brain:

- The brain has also auto-regulatory mechanisms that maintain blood flow if the BP drops mildly.
- If it drops below 60 mmHg, the compensatory mechanisms are overwhelmed with resultant cerebral ischaemia.

Kidneys: Changes similar to those described under hypovolaemic shock lead to renal failure.

Liver:

Under the effect of ischaemia and the chemical mediators cholestasis and hyperbilirubinaemia may develop, the so-called ICU jaundice

Gastrointestinal tract: lschaemia of the gut mucosa produces

1. Gastro-duodenal stress ulceration.
2. Gut barrier failure.

The result is translocation of bacteria and endotoxins from the colon lumen to the blood stream and further deterioration of the condition.

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Endocrine System

The endocrine glands are composed of the pituitary gland (the maestro), thyroid gland, parathyroid glands, suprarenal glands and the endocrine parts of pancreas and gonads. The functions of these glands are regulated by feeding pituitary hormones except for autonomous hyperfunction mostly of tumours and rarely hyperplasic glands.

APUD cells

- APUD is an acronym that stands for the ability of these cells for Amine Precursor Uptake, and then their Decarboxylation to produce a variety of hormones.
- These are endocrine cells of ectodermic origin arising from the neural crest and migrate during intrauterine life to different organs in the body.
- Examples of these cells include
    1. Pancreatic islet cells that secrete glucagon, insulin, and gastrin .
    2. Anterior pituitary cells that secrete ACTH.
    3. Adrenal medullary cells that secrete catecholamine.
    4. Parafollicular "C" cells of the thyroid that secrete calcitonin.
    5. Argentaffin cells in the bowel (Kulchitzki cells) that secrete serotonin.

Thyroid Gland

The functioning unit of the thyroid gland is the lobule supplied by single arteriole and consisting of 20-40 follicles , which are lined with cubical epithelium . The resting follicle contained colloid which thyroglobulin is stored .

Thyroid hormone synthesis

The normal thyroid gland is able to concentrate iodide from the blood at a rate of about 2 ug/hour.
Once within the thyroid follicular cells, the iodides are incorporated into the synthesis of the hormones Tri-iodo-thyronine (T3) and thyroxine (T4), the process being controlled by several enzymes in distinct steps.

- Trapping of inorganic iodide from the blood. This is an active process dependent on ATP.
- Oxidation of iodide into iodine by the peroxidase enzyme
- Binding of iodine with tyrosine by the tyrosinase enzyme to form mono and di-iodotyrosines (organification).
- Coupling of mono-iodotryosines and di-iodotyrosines to form T3 and T4 which unit with thyroglobulin and are stored in the follicles.

- Release of T3 and T4 into the circulation upon need. The major fraction of T3 or T4 in the blood is bound to plasma proteins (albumin, prealbumin and thyroid binding globulins). A minute fraction of T3 and T4 is present in a free form and this represents the functionally active fraction.
- Free T4 = 0.03-0.04% and free T3=0.2-0.5% of the total circulating hormones respectively), T3 is the quick acting, physiologically important hormone, being also produced by peripheral conversion from T4.
- Few mono and di-iodotyrosines are not coupled to form T3 or T4. They are deiodinated by dehalogenase enzyme. The released iodine is reused in thyroid hormone synthesis instead of being wasted.

Hypothalamo-pituitary-thyroid axis

Synthesis and liberation of thyroid hormones are controlled by the thyroid stimulating hormone (TSH) produced by the anterior pituitary. Its level assumes an inversely proportional relation to the level of circulating thyroid hormones (feedback mechanism). Thyrotropin releasing hormone (TRH) produced by the hypothalamus is a further stimulant to its production.

Histology of Parathyroid glands

a) The main cells are chief cells, which are of two types; light and dark; the latter is more active in parathyroid hormone (PTH) production.
b) Near puberty oxyphil cells and abundant fat cells appear.
c) Hyperplastic and neoplastic glands contain 'water-clear' cells.

Physiology of calcium of homeostasis

- The parathyroid glands secrete parathormone (PTH).
- Parathormone elevates serum calcium through bone resorption and increased calcium reabsorption in the renal tubules. Together with vitamin D they regulate calcium and phosphorus absorption.
- Vitamin D also increases serum calcium by promoting calcium absorption from the gut.
- On the contrary calcitonin from the Parafollicular cells of the thyroid decreases serum calcium through reversing the PTH effect on the bone and kidneys.
- PTH, calcitonin and vitamin D thus work in concert to modulate fluctuations in the level of serum ionized calcium.
- The serum calcium is made of 3 fragments
    - ionized 50%
    - protein bound 45%
    - complexed to organic anions 5%

  Hence the need for simultaneous assay of plasma proteins especially albumin.
- The factors regulating magnesium metabolism are not well known but PTH definitely plays a role.

- Bones are made of two components; 30% of bone matrix of collagen the major source of hydroxyproline, and 70% inorganic hydroxyapatite. Calcium in bone is divided into two major fractions
  - Labile fraction in physico-chemical equilibrium with the extracellular fluid.
  - Stable fraction bound to organic material; this type is removed only by resorption of bone by osteoclasts.

Adrenal Glands

The gland is formed of two parts; cortex and medulla.

The adrenal cortex

- It has three distinct-zones. From outside in these are
  1. *Zona glomerulosa:* The cells are arranged in whorls and secrete the mineralocorticoid aldosterone. The activity of this zone is under control of the renin-angiotensin system.
  2. *Zona fasciculate:* The cells are arranged in radial cords and bundles.
  3. *Zona reticularis:* The cells are arranged like a network.
- The zona fasciculata and reticularis secrete the glucocorticoids cortisol (hydrocortisone) and cortisone as well as androgens and a small amount of estrogens.
- The production of glucocorticoids is regulated by a negative feed-back mechanism that is mediated through the anterior pituitary hormone ACTH.

The adrenal medulla

- The medulla contains dark chromaffin cells which secrete the catecholamines (adrenaline and noradrenaline) .
- Embryologically; the chromaffin cells are of neuroectodermal origins that are derived from the neural crest. They are, therefore, part of the APUD system, whose tumours (apudomas) are either solitary or form a part of the multiple endocrine neoplasia syndrome.
- Ectopic medullary tissue may be present in the paraganglia, the organ of Zuckerkand at the origin of the inferior mesenteric artery, in the mediastinum , or in the retrogastric and retropancreatic areas.

Physiology of the breast

Hormonal control

Breast development is under the control of the following hormones:

1. Oestrogen, adrenocortical steroids, and growth hormone promote development of ducts.
2. Progesterone stimulates the growth of lobules.
3. Prolactin is essential for alveolar formation.

Physiological changes

- **At puberty:** The breast remains dormant until puberty. The onset of cyclical hormonal activity stimulates growth, branching of ducts, and formation of ductules.
- **Menstrual changes:** During the menstrual years the breast undergoes cyclic changes which can cause heaviness, discomfort, and increasing nodularity during the latter part of menstrual cycle.
- **During pregnancy:** there is marked lobular development. The high level of ovarian and placental oestrogen, however, inhibits lactation.
- **Lactation:** Following delivery, reduction of estrogen increases sensitivity of mammary epithelium to the lactational complex (prolactin, growth hormone, an cortisol) and milk is formed. Suckling stimulates the release of prolactin and oxytocin.
- Oxytocin in turn, stimulates the myoepithelial cells to eject milk into the terminal ducts.
- These effects are reversed by Weaning.
- **After menopause:** the lobules gradually disappear.

Salivary Glands

- Saliva secreted by the parotid differs from that secreted by the submandibular gland.
  - The parotid secretes serous fluid
  - The submandibular gland provides larger amount of high viscosity, calcium-rich fluid.
- Salivary secretion is a continuous day and night process, but is heightened during eating.
- Functions of the saliva:
  1. Food lubrication to allow swallowing.
  2. Cleaning the mouth.
  3. Starch digestion by the salivary amylase.
  4. It mediates taste sensation.

Lymphatic system

The lymphatic system has two main functions

- **Uptake, transportation, and return of fluid**, macromolecules and foreign substances from the interstitial space to the systemic circulation. It also helps in the clearing of debris from areas of tissue injuries. The amount of lymph returned to the circulation through the thoracic duct in 24 hours approximates the plasma volume. Lymphocytes and other cells enter the central circulation by its channels along with proteins and other large molecules. Chylomicrons and Lipoprotein complexes also enter the blood stream via the lymphatic system. In a 70 kg man at bed rest, the thoracic duct lymph flow approximates 2 liters daily with an average protein concentration of 4.8gm per 100 ml.
- **Protection** of the host by providing a filtration system that resists infection and impedes the spread of neoplastic diseases. There are three types of lymphocytes.
  - T-lymphocytes are derived from the thymus and mediate cellular immunity.
  - B-lymphocytes are generated independently of the thymus, they produce antibodies mediating humoural immunity.
  - A third type of heterogenous lymphocytes is known as null or non-B non-T type. The latter are sources of extramedullary haemopoiesis and can also form specialized cytotoxic lymphocytes that kill target cells in either the presence or the absence of specific antibodies.

  The different types of lymphatic cells are now identified largely by surface markers.

Visualization of lymphatics

Visual lymphangiography by injection of patent blue violet is performed for

1. Visualization of the lymphatics of a limb in cases of lymphedema to determine the condition of the lymphatic trunks and the level of lymphatic obstruction.
2. Visualization of the sentinel lymph node mainly in cases of breast cancer.

Isotope lymphography (lymphoscintigraphy)

99^{m}Tc labeled colloidal particles with antimony sulphide are injected in the first web, and the level of radioactivity is measured. It is then measured again after 45 and 90 minutes. The rate of disappearance of radioactivity is estimated. Normally, after 90 minutes, 40% of radioactivity at the injection site should have disappeared. After sometime, radioactivity over the inguinal and pelvic regions is estimated. A curve is drawn showing the relation between the level of radioactivity and time after injection. Normally there is step like rise of activity time curve at the inguinal region. Delineation of the lymphatic tree and lymph flow can be obtained.

Pediatric Physiology

Infants and children, in general, show major differences from adults. Their body systems have yet to develop and their full physiological functions and reserves are small. Thus it is easy for a small change to produce organ failure in one system; which may lead to failure of other systems.

Rate of change

Children are very fragile; a child can be moribund from meningitis within 24 hours or become dehydrated from gastroenteritis to the extent of peripheral circulatory failure in a day.

Temperature regulation

The small baby is easily affected by changes in environmental temperature. This is due to:

1. Thinner layer of subcutaneous fat.
2. Inadequate vasoconstriction of cutaneous vessels in response to cold.
3. Absent or rudimentary shivering and sweating mechanisms
4. Incomplete myelination of the CNS including the central heat regulating centre in the hypothalamus.

As a result, all premature babies and most neonates will require incubators or at least wrapping of limbs and body with cotton wool to minimize heat loss.

Body fluids and electrolytes

- 80% of the full-term baby's weight is water. This drops to 60% in adults.
- Maintenance of fluid and electrolyte balance is vital in the neonatal period. If oral intake is not feasible IV daily fluids are given.
- Daily fluid maintenance is given in the formula of 10% glucose in 0.18 percent saline.
- Potassium chloride (20 mmol/L) is added once urine flow is established.
- The fluid requirement of the neonate may be calculated according to the scheme
- All fluid losses, for example, nasogastric aspirate and ileostomy losses are replaced with normal saline with potassium chloride (20 mmol/L).
- The above are merely guidelines and each case must be assessed individually with repeated electrolyte estimations.

	Maintenance IV fluid/ day
Neonate	60 ml/kg to be raised by 10 ml/kg daily up to 100 ml
< 10 kg	100 ml/kg
>10 kg	100 ml/kg for first 10 kg + 50 ml for each additional kg of body weight

Renal adjustment

- Takes hours to days. As with adults and even more quickly, a baby may develop respiratory or metabolic acidosis or alkalosis.
- A simple formula that can be used to estimate the amount of bicarbonate needed to infuse in the first instance in the common condition of metabolic acidosis is
  Number of mmol HCO_3 = Base deficit X Wt in Kg/3.
- Proper correction of electrolyte and acid-base imbalance necessitates frequent monitoring of blood values several times daily.

Blood volume

- In a neonate, the blood volume is about 80 ml/kg body weight (70 ml/Kg in adults). Thus a 3.5 kg neonate will have 280 ml total blood volume.
- Three blood stained swabs during surgical operation will contain 30 ml of blood which constitute 10% of the total blood volume. Such loss is significant in neonates but very negligible in adults.
- Blood transfusion may be resorted to in restricted indications, e.g. blood loss, haemolytic anemia or severe anaemia.
- A general formula of 10 ml/kg of blood or 5 ml/kg of packed RBCS is usually adequate.

Respiratory system

- The lungs have sufficient capacity for postnatal survival at about 24 weeks gestation.
- After delivery, the lung matures rapidly but only about half of the alveoli are present at birth. It is worth remembering that the most energy consuming activity of the neonate is breathing.
- This explains the rapidity in which respiratory failure develops in babies with pneumonia.

Hepatic function

- The newborn liver is still immature.
- The most common example of this is the physiological jaundice that is brought about by the underdeveloped glucoronyltransferase system. Many other enzymes and functions are also involved, e.g. albumin, clotting factors and vitamin K.
- The liver acts also as a carbohydrate store in the form of glycogen.
- Even the full-term baby can not withstand starvation more than 6 hours without running the risk of hypoglycaemia.

Feeding

- Feeding may be by the following methods: breast, bottle, nasogastric tube, gastrostomy, trans-gastric duodenal or jejunal tube or intravenous fluid therapy.
- If the baby cannot tolerate enteral feeding for more than a week, total parenteral nutrition (TPN) is mandatory.

Central nervous system

- Myelination within the central nervous system is poorly developed at birth. The swings in heart and respiratory rate and temperature regulation are examples of the immature negative feedback loops at birth.
- The process of myelination not completed until the late teens.
- The development milestones of childhood are related to the gradual maturation of the cortical connections within the brain.

Pain relief and analgesia

- It was commonly stated that infants do not feel pain because of lack of central myelination. There is enough evidence to suggest that babies and small children produce physiological response to pain.
- It is also important to remember that the blood brain barrier is less efficient until 2 years of age due to incomplete myelination. As a result, fat-soluble drugs will permeate more freely into the cells in the brain in this age group. Thus opiates may produce respiratory depression at low doses. For example, morphine is given to adults in a dose of 0.2 mg/kg 6-8 hourly, but in the small infant 0.1 mg/kg 6-8 hourly is enough.

Metabolic Considerations of Nutrition

Maintaining a healthy nutritional status requires the adequate and balanced supplementation of calories proteins, vitamins, minerals, trace elements and water.

- **Calories** are obtained either by carbohydrates → 4 Kcal/g, or by fats→ 9 kcal/g.
- **Carbohydrates** are digested and then metabolized as glucose. The latter is the only source of energy for certain cells in the body which are the brain, red blood cells, and adrenal medulla.
- **Fats** are accepted as source of energy by other tissues and its administration is important to provide the body with essential fatty acids. Excess calorie intake is stored as fat.
- **Proteins** provide the building blocks of muscles as well as the raw material for the synthesis of enzymes and some of the hormones. Proteins are converted in the body to amino acids prior to their utilization. Essential amino acids are obtained only from dietary proteins. A practical way to assess the fate of ingested protein is to look at it in terms of its nitrogen content. The intake of 6.25 g of protein means 1g nitrogen thus the daily requirement of nitrogen is about 0.1 g/kg. If the intake of nitrogen exceeds its amount in urine, the body is said to be in a positive nitrogen balance, i.e. an anabolic state in which proteins are being formed if on the other hand the body is in negative nitrogen balance, then proteins are being catabolized and changed into glucose to supply energy, by the process of gluconeogenesis. Therefore for optimal utilization of proteins, enough calories should be supplied at a ratio of 100-250 kcal/1g nitrogen. At this ratio carbohydrates are said to have a protein-sparing effect.

Recommended daily Basal requirement		Calories produced by 1 g of	
	/ Kg		
Water (ml)	35	**Carbohydrates**	4 kcal
Non – protein (kcal)	30		
Proteins (g)	0.7	**Fats**	9 kcal
Nitrogen (g)	0.1		
Sodium (mmol)	1	**Proteins**	4 kcal
Potassium (mmol)	1		

Miscellaneous

Functions of the Skin

1. It forms a barrier against invasion by micro-organisms.
2. It prevents excessive loss of water from the body.
3. It helps in the regulation of body temperature by secretion of sweat.
4. Sensory receptors in the skin protect the body from injurious insults.
5. Formation of vitamin D.

Naevi

- Melanocytes develop from the neural crest and then migrate to lodge in between the basal cells of the epidermis.
- Their proportion to the basal cells is constant as 110 to 150 and their number per unit area of the skin is fixed irrespective of race or skin coloration.
- Differences in skin colour are due to the amount of melanin granules. Melanocytes form
- melanin pigment and transfer it to the adjoining keratinocytes through their dendritic processes.
- Melanoma is a true malignant neoplasm that arises from melanocytes.
- Various hamartomas can also arise from the melanocytes.

Protection from oral commensals

1. Regular desquamation and rapid replacement of surface cells.
2. Saliva that washes the oral cavity continuously.
3. The mild antibiotic activity of saliva.

Descent of the testis depends upon

1. Differential growth of the body; the cranial segment grows faster than the caudal segment.
2. Maternal chorionic gonadotrophins and pituitary gonadotrophic hormones play a definite role in the development and descent of the testis.
3. Contraction of the gubernaculum (fibromuscular tissue extending from the bottom of the scrotum to the lower pole of the testis) directs the testis towards t the scrotum.